THE PREPARATION OF SPECIFICALLY ^{2}H-LABELED BENZ[A]ANTHRACENES AND 7,12-DIMETHYLBENZ[A]ANTHRACENES[1]

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SUMMARY

The 2 + 4 cycloaddition reaction of 1,4-naphthoquinone and substituted styrenes was used to prepare 1-, 2-, 3-, and 4-bromobenz[a]anthracene-7,12-diones (BADs). The corresponding bromobenz[a]anthracenes (BAs) were prepared by aluminum tricyclohexoxide reduction of the diones. Lithiation with t-butyllithium followed by quenching with deuterium oxide gave the specifically ^{2}H-labeled BAs with deuterium incorporations of >95%. The 2-, 3-, and 4-bromo-7,12-dimethylbenz-[a]anthracenes (DMBAs) were prepared from the bromo BADs in moderate yield by the classical Grignard procedure. Lithium aluminum deuteride reduction gave the ^{2}H-DMBAs. An alternate synthesis from 3,4-dihydrobenz[a]anthracene 1-(2H)-one was used for the preparation of 1- and 2-^{2}H BAs and DMBAs.

Key Words: Synthesis, Benz[a]anthracenes, 7,12-dimethylbenz[a]anthracenes, specific deuteration, 2 + 4 cycloaddition

INTRODUCTION

Polycyclic aromatic hydrocarbons have been shown to require metabolic activation before they can induce cancers in mammalian tissues.[2] In support of

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0362-4803/81/030331-15$01.00

Received October 22, 1979
Revised January 11, 1980

studies directed toward the elucidation of the biochemical mechanisms of this activation, workers in our own[3] and other laboratories[4] have reported the synthesis of possible metabolites of both the potent carcinogen 7,12-dimethylbenz[a]anthracene (DMBA) (1) and its weakly carcinogenic analog benz[a]anthracene (BA) (2).

In this report we describe a new relatively simple and direct route to the synthesis of specifically mono-deuterated derivatives of 1 and 2. These compounds will provide substrates for further elucidation of the mechanisms of metabolism of 1 & 2. In particular, they can help distinguish whether the primary route to the phenolic derivatives of 1 & 2 is direct hydroxylation or through the formation of arene oxides followed by the "NIH Shift."[5]

Previous routes to specifically deuterated polycyclic aromatics have been limited to those sites which are most reactive toward electrophilic aromatic substitution.[6] In previous communications we have reported the development of a new, general route to benz[a]anthracene-7,12-diones (BAD's) (3) based upon the (2 + 4) cycloaddition reaction of 1,4-naphthoquinones to styrenes.[7]

The conversion of 3 to 1 or 2 appeared to be the most promising route. The commercially available, mono-halogenated styrenes thus provide the basis for our synthesis.

RESULTS AND DISCUSSION

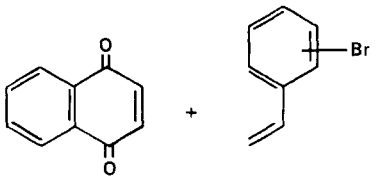
The bromo-diones (3a-d) were prepared by heating a mixture of equimolar amounts of 1,4-naphthoquinone, the appropriate bromostyrene, and chloranil in toluene for 2 to 4 weeks.

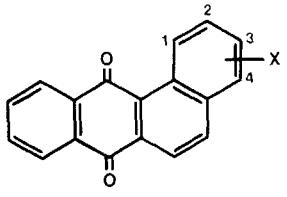
4-Bromostyrene gave a 40% yield of 2-bromoBAD (3b) as the sole product while 3-bromostyrene gave a 39% yield of a 12:1 mixture of 3-bromoBAD (3c) and 1-bromoBAD (3a). Separation of 3a from 3c and purification of 3b was by chromatography on a silica gel column using a slow gradient of hexane to 50:50 hexane-benzene.

As we have previously reported,[7] 2-bromostyrene gave 4-bromoBAD (3d) in 30% yield; however, this compound is most conveniently prepared by bromination of 3 by the method of Badger and Gibb.[8a]

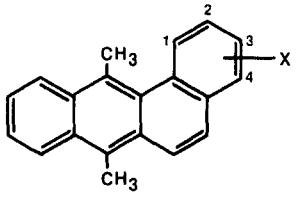
The structural assignment of the three new bromoBADs proceeds logically from considerations of the structure of the starting styrenes and from the geometry required by the transition state for the 2 + 4 cycloaddition reaction. The bromine atom of 4-bromostyrene is situated symmetrically with respect to the exocyclic double bond and this isomer would be expected to give only 3b. The reaction of 3-bromostyrene could adopt either the orientation which would lead to 3a or that which would give 3c. The steric crowding between the bromine and the carbonyl accounts for the 12:1 isomer ratio observed in this case. The spectroscopic data support the assigned structures. The fingerprint region of the infrared spectrum (1000-700 cm^{-1}) of each BAD was consistent with previously observed values for the corresponding chloroBADs.[7] Both 3b and 3c showed strong peaks in their mass spectrum for the molecular ions (m/z 336 and 338) while 3a gave weak molecular ions but had a strong M^+-Br fragment at m/z 257. Brown and Thomson[10] have established that the proton magnetic resonance (PMR) absorption for the 1-proton of 3 occurs at 9.72 δ. As was found for the chloroBADs this peak confirms the structural assignments. Compound 3a lacks this peak as would be expected for 1-bromo substitution. In 3b the proton appears as a broad singlet while in 3c it appears as a double (J=9Hz).

Reduction of 3b-d to 2b-d was effected with aluminum tricyclohexoxide in cyclohexanol at reflux by the method of Ahmed et al.[8b] While this procedure was somewhat more tedious than the two-step method used by Badger and Gibb,[8a] it was preferred for this transformation. Both Kloetzel et al.[11] and Nes and Ford[12] found that Badger's conditions gave 2 as the major product of the reduction of 3d. Special precautions were required for the reduction of 3a to 2a, even using Ahmed's procedure. When the reaction was carried out at reflux, the major product was 2. When the reaction mixture was maintained below 90°, however, 2a was isolated in 63% yield.

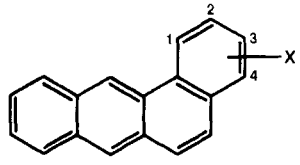




3 X = H
3a X = 1-Br
3b X = 2-Br
3c X = 3-Br
3d X = 4-Br
6 X = 4-Cl



1 X = H
1a X = 1-Br
1b X = 2-Br
1c X = 3-Br
1d X = 4-Br
5a X = 1-^{2}H
5b X = 2-^{2}H
5c X = 3-^{3}H
5d X = 4-^{2}H
8 X = 4-CH_3

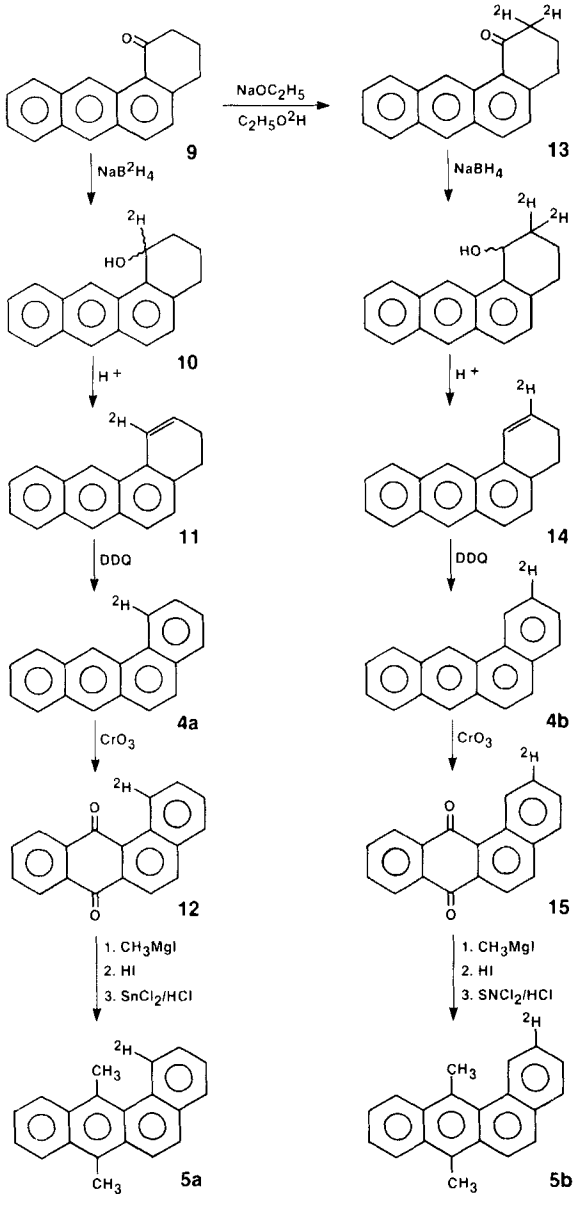


2 X = H
2a X = 1-Br
2b X = 2-Br
2c X = 3-Br
2d X = 4-Br
4a X = 1-^{2}H
4b X = 2-^{2}H
4c X = 3-^{3}H
4d X = 4-^{2}H
7 X = 4-Cl

Lithiation, followed by quenching with deuterium oxide, proved satisfactory for the introduction of ^2H into 2a-d. In the case of 2d, 4d was obtained in 83% yield. The mass spectrum of this material showed a molecular ion at m/z 229, the peak at 228 showing only 15% of the intensity of the molecular ion. In 2 the m/z 227 peak is about 12% of the molecular ion. From these data we conclude the ^2H incorporation was >95%. Similar results were obtained for 2a-c.

The bromoDMBAs (1b-d) were prepared from the bromoBADs 3b-d using methyl magnesium iodide following the procedure of Descamps and Martin.[9] While these workers converted 1d to 8 by lithiation, problems were encountered in applying this method to the preparation of ^2H-DMBAs. In particular when 1d was subjected to exactly the same reaction conditions which had been used for the conversion of 2d to 4d, a material was obtained which had a PMR that showed diminished intensities for the methyl protons. Since this could arise from scrambling of the aryl anion, we elected to introduce the label by the use of lithium aluminum deuteride. Reduction of 1b-d with lithium aluminum deuteride gave the desired ^2H-DMBAs in 80-90% yields. Estimation of the isotopic purity by mass spectrometry gave deuterium incorporations of >93%.

While this route has proved quite facile for the preparation of 2-, 3-, and 4-substituted compounds, the low yield of 3a by the dione-quinone method led us to investigate alternative methods for the synthesis of 4a and 5a. Yang et al.[14] reported the synthesis of 3-^2H-benzo[a]pyrene from 1,6,10b, 11,12,12a-hexahydrobenzo[a]pyrene-3-(2H)-one. We have applied a similar sequence to the synthesis of ^2H-BAs and DMBAs through the use of 3,4-dihydrobenz[a]anthracene-1-(2H)-one (9), which is commercially available. Compound 9 was readily reduced to 1-^2H-1-hydroxy-1,2,3,4-tetrahydrobenz[a]anthracene (10) with sodium borodeuteride. The deuterated alcohol 10 was not isolated; rather the crude product was dehydrated with p-toluenesulfonic acid (TSOH) to give 1-^2H-3,4-dihydrobenz[a]anthracene (11) in 56% yield.


NaOC2H5
C2H5O2H
NaB2H4
NaBH4
H+
DDQ
CrO3
1. CH3MgI
2. HI
3. SnCl2/HCl
3. SNCl2/HCl
9
10
11
4a
12
13
14
4b
15
5a
5b

Aromatization of 11 was accomplished by refluxing with DDQ in benzene to give 1-^{2}H-benz[a]anthracene (4a) in 90% yield. Oxidation of 4a with chromium trioxide in acetic acid gave 1-^{2}H-benz[a]anthracene-7,12-dione (12) in 42% yield. Conversion of 12 to 1-^{2}H-7,12-dimethylbenz[a]anthracene (5a) was accomplished with methymagnesium iodide.

Equilibration of 9 with ethanol-O-^{2}H and sodium ethoxide gave 2,2-bis-^{2}H-3,4-dihydrobenz[a]anthracene-1-(2H)-one (13). Compound 13 was reduced with sodium borohydride followed by dehydration with TSOH to give 2-^{2}H-3,4-dihydrobenz[a]anthracene (14), which was aromatized as described above to give 2-^{2}H-benz[a]anthracene (4b). Compound 4b was oxidized to 2-^{2}H-benz[a]-anthracene-7,12-dione (15) and then converted to 2-^{2}H-DMBA (5b).

The amounts of ^{2}H incorporation into 4a, 4b, 5a, 5b, 12, and 15 were equal to, or greater than, 97% as determined by mass spectrometry.

EXPERIMENTAL

All melting points were determined using a Fisher-Johns hot-stage apparatus and are uncorrected. Mass spectra were taken on a Finnegan 3300 or a VG Micromass ZAB 2-F Mass Spectrometers. PMR spectra were taken in $CDCl_3$ on a Varian XL-100 instrument using Fourier Transform with TMS as an internal standard. Infrared spectra were recorded on a Perkin Elmer 467 spectrophotometer as KBr pellets. Microanalyses were by Galbraith Laboratories, Knoxville, Tenn.[13]

General Procedure for the Preparation of the Bromobenz[a]anthracene-7,12-diones (3a-c)

A suspension of 13g of chloranil, 8g (0.05 mole) of 1,4-napthoquinone, and 12g (0.065 mole) of the appropriate styrene in 100 mL of toluene was stirred at 95-100° for 14 to 28 days. The solvent was evaporated under reduced pressure and the residue was treated with 100 mL of a 5% solution of alcoholic potassium hydroxide. Oxygen was bubbled through this mixture for 24 hr. The suspension was neutralized with hydrochloric acid, methylene chloride was added to dissolve

the solids and the organic phase was washed with water. After drying ($MgSO_4$) and removal of the solvent, the material was chromatographed on Mallinckrodt Silica gel CC-7 with a gradient of hexane to hexane-benzene (1:1). Final purification was by recrystallization from acetic acid.

1-Bromobenz[a]anthracene-7,12-dione (3a) was obtained in 3% yield (493 mg) from the reaction of 1,4-naphthoquinone and 3-bromostyrene, mp 189-190°C. IR: 1656 (C=O), 1590, 1427, 1300, 1275, 850, 845, 755, 715, and 701 cm^{-1}. Mass spectrum: m/z, (relative intensity); 338 (0.13), 336 (0.08), (M^+) 257 (100), (M^+ - Br). PMR: no peaks above 8.5 δ.

2-Bromobenz[a]anthracene-7,12-dione (3b) was obtained in 40% yield (6.74 g) from the reaction of 1,4-naphthoquinone with 4-bromostyrene, mp 261-262°C. IR: 1655 (C=O), 1580, 1300, 1270, 855, and 710 cm^{-1}. Mass spectrum: m/z (relative intensity) 338 (75.8), 336 (83.8), (M^+ doublet); 257 (75.6), (M^+ - Br). PMR: (δ) 9.04 (broad d, 1H).

3-Bromobenz[a]anthracene-7,12-dione (3c) was obtained in 36% yield (6.06 g) from the same reaction as 3a, mp 222-223°C. IR: 1665 (C=O), 1585, 1450, 1337, 1305, 1270, 992, 872, 800, and 712 cm^{-1}. Mass spectrum: m/z (relative intensity); 338 (73.46), 336 (77.38), (M^+ doublet); 257 (50.48, (M^+ - Br). PMR: (δ) 9.75 (d, 1H).

General Procedure for the Preparation of the Bromobenz[a]anthracenes (2b-d)

In a typical experiment, aluminum tricyclohexoxide was prepared by the addition of 100 mg of aluminum wire, 0.5 mL of carbon tetrachloride, and approximately 3 mg of mercuric chloride to 20 mL of dry cyclohexanol. This mixture was heated at reflux under a nitrogen atmosphere until all of the aluminum was consumed (about 2 hr). To this freshly prepared solution was added 168 mg (0.5 mmole) of the dione.

The resulting mixture was then heated at reflux until thin layer chromatography showed that all of the dione had disappeared (1 to 3 days). The hot solution was poured into ice water, acidified with concentrated hydrochloric acid, and stirred for 3 hr. The aqueous mixture was extracted with methylene

chloride, the organic layer washed once with 5% aqueous sodium bicarbonate, twice with water, and dried over magnesium sulfate. Evaporation of the methylene chloride gave a suspension of the benz[a]anthracene in cyclohexanol from which the remaining solvent was removed by vacuum distillation. Chromatography on neutral alumina using benzene-hexane (1:1, v/v) followed by recrystallization from benzene, gave the pure product.

2-Bromobenz[a]anthracene (2b) was obtained in 59% yield, mp 159.5-161°C. IR: 888, 878, 829, and 750 cm^{-1}. Mass spectrum: m/z (relative intensity) 308 (24.38) and 306 (24.85), (M^{+} doublet). PMR: (δ) 9.1 (s,1); 8.96 (s,1); 8.4 (s,1); and 8.3-7.5 (m,8).

3-Bromobenz[a]anthracene (2c) was obtained in 80% yield, mp 189-191°C. IR: 900, 889, 830, and 744 cm^{-1}. Mass spectrum: m/z (relative intensity); 308 (43.64) and 306 (44.28), (M^{+} doublet). PMR: (δ) 9.02 (s,1); 8.58 (d,1); 8.30 (s,1); 8.2-7.4 (m,8).

4-Bromobenz[a]anthracene (2d) was obtained in 63% yield, mp 210-211°C (lit.[8a] 210-211°C).

Preparation of 1-bromobenz[a]anthracene (2a). This compound was prepared according to the general procedure given above with the exception that after the addition of the dione the reaction temperature was kept at 85-90°C. The product, (2a), was obtained in 28% yield, mp 167-168°C. IR: 890, 881, 834, and 754 cm^{-1}. Mass spectrum: m/z (relative intensity); 308 (12.78) and 306 (13.02). PMR: (δ) 9.28 (s,1); 8.25 (s,1); 8.1-7.4 (m,9).

General Procedure for the Preparation of the ^{2}H-Benz[a]anthracenes (4a-d)

A solution of 153 mg (0.5 mmole) of the appropriate bromobenz[a]anthracene in 10 mL of dry tetrahydrofuran was cooled to -78°C in an inert atmosphere. To this mixture was added dropwise 1 mL of a 1.9 M solution of t-butyllithium in pentane. After the additon was complete, the cooling bath was removed and the reaction mixture was allowed to come slowly to room temperature. After 2 hr, the reaction was quenched with 5 mL of deuterium oxide. The resulting mixture was diluted with 10 mL of ethyl ether and extracted with 10% hydrochloric acid.

The organic layer was washed twice with water and dried over $MgSO_4$. Removal of the solvent gave a yellow solid which was purified by chromatography on silica gel using benzene-hexane (1:1) as solvent followed by recrystallization from benzene.

1-^{2}H-benz[a]anthracene (4a) was obtained in 61% yield. Mass spectrum: m/z (relative intensities); 229 (100), (M^+); 228 (9.13). PMR: (δ) 9.09 (s,1); 8.19 (s,1); 8.13-7.43 (m,9).

2-^{2}H-benz[a]anthracene (4b) was obtained in 85% yield. Mass spectrum: m/z (relative intensities); 229 (100) (M^+); 228 (11.34). PMR: (δ) 9.15 (s,1); 8.79 (s,1); 8.42 (s,1); 8.2-7.4 (m,8).

3-^{2}H-benz[a]anthracene (4c) was obtained in 79% yield. Mass spectrum: m/z (relative intensities); 229 (100) (M^+); 228 (11.49). PMR: (δ) 9.18 (s,1); 8.85 (d,1); 8.39 (s,1) 8.2-7.4 (m,8).

4-^{2}H-benz[a]anthracene (4d) was obtained in 83% yield. Mass spectrum: m/z (relative intensities); 229 (100) (M^+); 228 (10.20). PMR: (δ) 9.12 (s,1); 8.81 (d,d,1); 8.34 (s,1); 8.2-7.4 (m,8).

The mass spectrum of benz[a]anthracene (2) gave 228 (100) (M^+); 228 (5.85). Using the mass spectroscopic data the isotopic purities were calculated to be 97% for 4a, 95% for 4b and 4c, and 96% for 4d.

General Procedure for the Preparation of the Bromo-7,12-dimethylbenz[a]-anthracenes (1b-d)

(Method of Descamps and Martin.[9]) A solution of methylmagnesium iodide, prepared from 300 mg of magnesium and 2 mL of methyl iodide in 8 mL of dry ether, was added dropwise to a suspension of 250 mg (0.74) of the appropriate bromoBAD in 15 mL of dry benzene. After a few minutes the dione had dissolved and the solution was pale yellow. The solution was stirred at room temperature for 2 hr and cooled to 0°C in ice. A solution of 3 mL of hydriodic acid (57%) in 10 mL of methanol was added slowly to the reaction mixture followed by the addition of 15 mL of glacial acetic acid. This mixture was allowed to stand at 0°C overnight and the orange, crystalline precipitate was collected by

filtration. These wet crystals were immediately dissolved in a mixture of 15 mL of dioxane and 1 mL of hydrochloric acid and reduced by the addition of a solution of 2.5 g of stannous chloride in 12 mL of dioxane and 8 mL of hydrochloric acid. This mixture was heated at reflux briefly, cooled to room temperature, and flooded with water. The precipitate of the bromo DMBA was collected and recrystallized from benzene-ethanol.

2-Bromo-7,12-dimethylbenz[a]anthracene (1b) was obtained in 73% yield, mp 110.5-111.5°C. IR: 868, 805, and 745 cm^{-1}. Mass spectrum: m/z (relative intensities); 336 (54.66) and 334 (56.22) (M^+ doublet) PMR: (δ) 8.62 (s,1); 8.5-7.4 (m,8); 3.35 (s,3); 3.05 (s,3).

3-Bromo-7,12-dimethylbenz[a]anthracene (1c) was obtained in 69% yield, mp 167-168°C. IR: 870, 827, and 742 cm^{-1}. Mass spectrum: m/z (relative intensities); 336 (43.89) and 334 (41.86) (M^+ doublet) PMR: (δ) 8.5-7.3 (m,9); 3.15 (s,3); 3.05 (s,3).

4-Bromo-7,12-dimethylbenz[a]anthracene (1d) was obtained in 80% yield, mp 151-152°C (lit.[9] 150-151.5°C).

General Procedure for the Preparation of the ^2H-DMBA's (5b-d)

A dry 10 mL 2-necked flask was fitted with a rubber spectum and a reflux condenser fitted with a nitrogen bubbler. The flask was charged with 70 mg of lithium tetradeuteroaluminate and 3 mL of freshly distilled THF. A solution of 90 mg (0.3 mmole) of the bromo DMBA in 2 mL of dry THF was added through the septum and the resulting mixture was heated at reflux for 3 hr. The excess $LiAl^2H_4$ was destroyed by the cautious addition of 50-50 mixture of deuterium oxide and THF. Extraction with ether and water, drying of the ether layer, and removal of the solvent gave the crude hydrocarbon which was purified by chromatography [silica gel with benzene-hexane (1:1)].

2-^2H-7,12-dimethylbenz[a]anthracene (5b) was prepared in 75% yield. Mass spectrum: m/z (relative intensities); 257 (100) (M^+); 256 (12.43). PMR: (δ) 8.62 (s,1); 8.5-7.3 (m,8); 3.35 (s,3); 3.05 (s,3).

3-^{2}H-7,12-dimethylbenz[a]anthracene (5c) was prepared in 68% yield. Mass spectrum: m/z (relative intensities); 257 (100) (M^+); 256 (11.45). PMR: (δ) 8.5-7.3 (m,9); 3.32 (s,3); 3.10 (s,3).

4-^{2}H-7,12-dimethylbenz[a]anthracene (5d) was prepared in 78% yield. Mass spectrum: m/z (relative intensities); 257 (100) (M^+); 256 (13.15). PMR: (δ) 8.5-7.3 (m,9); 3.32 (s,3); 3.09 (s,3).

Preparation of 1-^{2}H-3,4-dihydrobenz[a]anthracene (11).

To a stirred solution of 400 mg of sodium borodeuteride in 60 mL of dry methanol and 20 mL of dry tetrahydrofuran (THF) was added in one portion 492 mg (2.0 mmole) of 9. The resultant solution was stirred at room temperature for 4 hr at which time 100 mL of cold water was added. The resultant mixture was extracted with 100 mL of benzene. The organic layer was dried (Na_2SO_4) and a catalytic amount of p-toluenesulfonic acid added. The resulting solution was heated at reflux for 2 hr and then stirred at room temperature overnight. Extraction with water, followed by drying ($MgSO_4$) and removal of the solvent gave a yellow oil which solidified on standing. Chromatography on silica gel [hexane benzene (2:1)] gave yellow needles, mp 97-98.5°C. Yield: 261 mg (56%). PMR: (δ) 8.62 (s, 1); 8.36 (s, 1); 8.2-7.3 (m, 6); 6.32 (broad t, 1); 3.0 (m, 2), and 2.4 (m, 2). Mass spectrum: m/z (relative intensities); 231 (100) (M^+); 230 (61.3).

Preparation of 1-^{2}H-benz[a]anthracene (4a).

A solution of 112 mg (0.48 mmole) of 11 and 300 mg of DDQ in 15 mL of benzene was heated at reflux under a nitrogen atmosphere for 1.5 hr. After cooling, the mixture was chromatographed on a short alumina column using benzene as the eluting solvent. Removal of solvent followed by recrystallization from benzene gave 100 mg (90%) of 4a, mp 158-159°C. This material was identical in all respects with 4a as prepared from 1-bromobenz[a]anthracene. Mass Spectrum: m/z (relative intensities); 229 (100) (M^+); 228 (9.1).

Preparation of 1-^{2}H-benz[a]anthracene-7,12-dione (12).

A solution of 50 mg (0.22 mmoles) of 1-^{2}H-BA (4a) in 7 mL acetic acid was added dropwise to a 10°C solution of 100 mg of CrO_3 in two drops of water and 5 mL acetic acid. When all the BA had been added, the reaction mixture was allowed to warm to room temperature (1 hr). The excess CrO_3 was destroyed with methanol, the mixture diluted with 50 mL water, and extracted with benzene. The organic layer was washed twice with 10% $NaHCO_3$ and dried. Removal of solvent gave a yellow solid which was purified by chromatography on silica gel using benzene as the eluting solvent. Isolation of the major fraction gave 24 mg (42%) of 1-^{2}H-BAD (12), mp 169-170°C. Mass spectrum: m/z (relative intensities); 259 (100) (M^+) 258 (25.4).

1-^{2}H-7,12-dimethylbenz[a]anthracene (5a).

A solution of methylmagnesium iodide, prepared from 40 mg of magnesium and 0.2 mL of methyl iodide in 1 mL of dry ether, was added dropwise to 24 mg (0.09 mmole) of 12 in 1 mL benzene. The solution was stirred at room temperature for 1 hr and cooled to 0°C. A solution of 0.3 mL of hydriodic acid (57%) in 1 mL methanol was added slowly to the reaction mixture followed by the addition of 2.4 mL of glacial acetic acid. This mixture was allowed to stand at 0°C overnight, and the orange, crystalline precipitate collected by filtration. The wet crystals were immediately dissolved in a mixture of 1.2 mL of dioxane and 0.1 mL of hydrochloric acid and reduced by the addition of a solution of 18 mg of stannous chloride in three drops of dioxane and ten drops of hydrochloric acid. This mixture was heated to boiling, cooled, and flooded with water. The precipitate was collected and chromatographed on silica gel using benzene to give 12 mg (52%) of 1-^{2}H-DMBA, mp 121-122°C. Mass spectrum: m/z (relative intensities); 257 (M^+) (100); 256 (8.2). PMR: (δ) 8.5-7.3 (m,9); 3.32 (s,3); 3.10 (s,3).

Preparation of 2,2-bis-^{2}H-3,4-dihydrobenz[a]anthracene-1-(2H)-one (13).

A solution of 200 mg of sodium and 469 mg of 9 in 50 mL of ethanol-O-^{2}H was stirred at room temperature in a nitrogen atmosphere for 24 hr. The solvent

was removed at reduced pressure and fresh ethanol-O-^{2}H was added and this new solution stirred for 24 hr. The solution was diluted with deuterium oxide, neutralized with a few drops of hydrochloric acid, and the product isolated by extraction with ether. Removal of the solvent gave 455 mg (97%) of 13, mp 114-116°C. Mass spectrum: m/z, 248 (M^+). PMR: (δ) 8.38 (s, 1); 8.3-7.2 (m,7); 2.83 (t,2,J=7H_z); 2.22 (t,2,J=7H_z).

Preparation of 2-^{2}H-benz[a]anthracene (4b).

Compound 13 was reduced under the same conditions as described for 9 with the exception that sodium borohydride was employed as the reducing agent. After dehydration with TSOH, the crude dihydro compound 14 was not purified but was aromatized as for compound 11 to give a 51% overall yield of 4b, mp 158-159°C. Mass Spectrum: m/z (relative intensities); 229 (100) (M^+); 228 (8.6).

2-^{2}H-benz[a]anthracene-7,12-dione (15) was prepared from 4b exactly as 12 in 62% yield, mp 169-170°C. Mass Spectrum: m/z (relative intensities); 259 (100) (M^+); 258 (24.9).

2-^{2}H-7,12-dimethylbenz[a]anthracene (5b) was prepared from 15 exactly as 5a in 54% yield, mp 121-122°C. Mass Spectrum: m/z (relative intensities); 257 (100) (M^+); 256 (8.2).

ACKNOWLEDGEMENTS

We thank Dr. D.J. Wilbur for determination of the PMR spectra and Mr. S.S. Huang and Dr. G.A. McClusky for determination of the mass spectra.

This research was supported by Contract NO1-CO-75380 with the National Cancer Institute, NIH, Bethesda, Maryland 20205.

REFERENCES

1. Presented in part before the 176th National Meeting of the American Chemical Society, Organic Division, Miami Beach, Fl., Sept. 1978, Abstract No. 109.

2. Moschel, R.C., Baird, W.M., and Dipple, A. - Biochem. Biophys. Res. Commun. 76: 1092 (1977)

3. A. Manning, W.B., Muschik, G.M., and Tomaszewski, J.E. - J. Org. Chem. 44: 699 (1979)

B. Muschik, G.M., Tomaszewski, J.E., Sato, R.I., and Manning, W.B. - J. Org. Chem. 44: 2150 (1979)

4. A. Morreal, C.E. and Alks, V. - J. Chem. Eng. Data. 22: 118 (1977)

B. Newman, M.S., Khanna, J.M., Kanakarijan, K., and Kumar, S. - J. Org. Chem. 43: 2553 (1978)

5. See for example, Daly, J.W., Jerina, D.M., and Witkop, B. - Experientia 28: 1129 (1972)

6. Yang, S.K., Roller, P.P., Fu, P.P., Harvey, R.G., and Gelboin, H.V. - Biochem. Biophys. Res. Commun. 77: 1176 (1977)

7. Manning, W.B., Tomaszewski, J.E., Muschik, G.M., and Sato, R.I. - J. Org. Chem. 42: 3465 (1977)

8. A. Badger, G.M. and Gibb, A.R.M. - J. Chem. Soc. 799 (1949)

B. Ahmed, F.U., Rongarajon, T., and Eisenbaum, E.J. - Org. Prep. Proced. Int. 7: 267 (1975)

9. Descamps, G. and Martin, R.H. - Bull. Soc. Chim. Belges. 61: 223 (1952)

10. Brown, P.M., and Thomson, R.H. - J. Chem. Soc., Perkin Trans 1: 997 (1976)

11. Kloetzel, M.C., Broussalian, G.L., Warren, C.K., and Field, J.B. - J. Org. Chem. 26: 1748 (1960)

12. Nes, W.R. and Fond, D.L. - J. Amer. Chem. Soc. 85: 2137 (1963)

13. All new compounds gave satisfactory elemental analyses.

14. Yang, S.K., Roller, P.P., Fu, P.P., Harvey, R.G. and Gelboin, H.U. - Biochem. Biophys. Res. Comm., 77, 1176 (1977).